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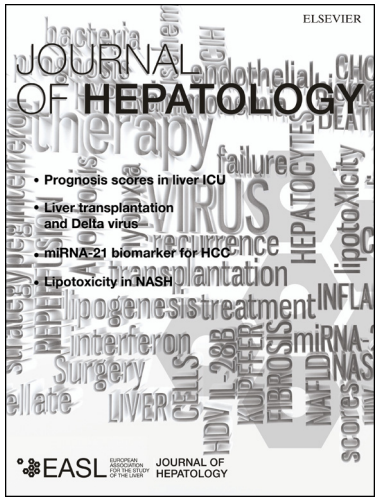

Development and validation of a polycystic liver disease-complaint-specific-assessment (POLCA)

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Revision 3

Development and validation of a polycystic liver disease-complaint-specific-assessment (POLCA)

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List of abbreviations: polycystic liver disease (PCLD); somatostatin analogue (SA); liver transplantation (LTx); PCLD-Complaint-Specific-Assessment (POLCA); Short-Form (36) Health Survey (SF36); computed tomography (CT); liver volume (LV); lanreotide (LAN); mTOR: mammalian Target of Rapamycine; autosomal dominant polycystic kidney disease (ADPKD); autosomal dominant polycystic liver disease (ADPLD); Food and Drug Adminsitration (FDA); physical component summary (PCS); mental component summary (MCS); gastro-oesophagal reflux disease (GERD); Health Related Quality of Life (HRQL); interquartile range (IQR).

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ABSTRACT

Background & Aims: Polycystic liver disease (PCLD) may lead to extensive hepatomegaly and invalidating complaints. Therapeutic decisions, including somatostatin-analogues (SA), (non)-transplant surgery are besides the existence of hepatomegaly, also guided by the severity of complaints. We developed and validated a self-report instrument to capture the presence and severity of disease specific complaints for PCLD.

Methods: The study population consisted of 129 patients. Items for the PCLD-Complaint-Specific-Assessment (POLCA) were developed based on chart review of symptomatic PCLD patients (n=68) and literature; and discussed during expert-consensus-meetings. 61 patients who needed therapy were asked to complete the POLCA and the Short Form Health Survey (SF-36Version2) at baseline and after 6 months of SA-treatment. CT-scans were used to calculate liver volumes (LV). Factor analysis was conducted to identify subscales and remove suboptimal items. Reliability was assessed by Cronbach's alpha. Convergent, criterion validity and responsiveness were tested using pre-specified hypotheses.

Results: In the validation group (n=61), 47 received lanreotide (LAN) and 14 were offered LAN as bridge to liver transplantation (LTx). Factor analysis identified 4 subscales which correlated with the Physical Component Summary (SF36). Baseline POLCA scores were significantly higher in LTx-listed patients. In contrast to SF36V2, POLCA paired observations in 47 patients demonstrated that 2 subscales lowered significantly and 2 borderline. LV reduction ≥120mL resulted in a numerical more pronounced relative decrease of all scores.

Conclusions: In contrast to SF36V2, the POLCA shows good validity and responsiveness to measure complaint severity in PCLD.

Word count: 239

Key words: hepatomegaly, somatostatin-analogues; liver transplantation; health-related-quality of life

Introduction

Polycystic liver disease (PCLD) is a chronic inherited disorder in which numerous fluid-filled hepatic cysts are scattered throughout the liver. PCLD is the most frequent extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD). The second cause of PCLD is autosomal dominant polycystic liver disease (ADPLD), in which patients do not suffer from renal failure and only present with liver cysts. The natural history of PCLD, regardless of the genetic mutation, is similar [1-3]. Most of the patients with PCLD stay asymptomatic, but 2-5% of patients will develop symptomatic hepatomegaly as a result of the continuous increase in volume and number of liver cysts. The most frequently reported symptoms in the literature include abdominal distension, early satiety, abdominal pain, and finally severe malnutrition which can be lethal. Some of these patients develop portal hypertension, ascites or Budd-Chiari like syndrome, but these complications are rather uncommon [2].

To reduce liver volume and improve complaints, several surgical techniques have long been the mainstream, including aspiration-sclerotherapy, laparoscopic or laparotomic fenestration and partial liver resection [4]. In patients with massive hepatomegaly and extreme invalidating symptoms, the only curative therapeutic option is liver transplantation (LTx) [5,6]. Pharmacological treatment of PCLD only became available five years ago. We and others showed that somatostatin-analogues (SA), i.e. lanreotide and octreotide, decrease liver volume [7-10]. In addition, we recently demonstrated that a reduction of ≥120mL in liver volume after 6 months has a high positive predictive value of improving complaints, a reduction which lies above the 95% upper limit of the confidence intervals of the differences in LV assessed by two software methods measuring the same LV [11]. Also mTOR inhibitors might reduce liver volume, although the data are less robust and

combination of octreotide and everolimus did not increase the LV reducing effect of octreotide alone [3,12].

For the majority of patients, the hepatomegaly induced complaints represent the most important (referral) reason for medical or surgical treatment. Until now, this evaluation is almost exclusively made by physicians in a non-standardized way. Currently, there is no disease specific questionnaire that *(i)* assesses presence, severity and impact of complaints in a standardized, valid way; *(ii)* can be used to assess the effect of pharmacological therapy; *(iii)* and finally is suitable to guide treatment decisions.

We aimed to develop and validate a questionnaire, -the PCLD Complaint Specific Assessment (POLCA)-, intended to assess the specific complaints from the perspective of PCLD patients associated with hepatomegaly.

Patients and methods

In line with the FDA guidelines on development of patient reported outcome measures, we first established a conceptual framework in which we described the item generation process and psychometric properties (Supplementary materials A) [13,14]. In line with the conceptual framework on symptom experience of Leventhal and colleagues, the questionnaire should be able to capture both the presence as well as the severity of complaints [15,16].

Study design

Item selection and content validity:

We constructed an exhaustive list of items likely to represent complaints of hepatomegaly that could be perceived by patients with symptomatic PCLD, using two

sources: *(i)* analysis of medical charts of 68 patients (creation group) referred for treatment between (1995-2007); and *(ii)* extensive literature search in Pubmed, extracting complaints of PCLD reported in studies published between January 1997 and August 2010. Using search terms referring to the disease, its treatment forms and aspects of health-related quality of life, 15 articles were identified for data extraction [4,5,7,8,17-27].

In total, 27 candidate items were identified that were subsequently reviewed for relevance by an independent expert panel (3 hepatologists, 2 nephrologists, and 1 abdominal transplant surgeon) and agreed upon during consensus meetings.

Next, based on evidence on optimal scaling of self-report instruments, a questionnaire was created with labeled Likert-type responses ranging from 0 to 5 for presence (0= symptom not occurring; 5= symptom present all the time), as well as for severity (0= not; 5= extreme severe) [28]. All items in this questionnaire were then critically evaluated by the same 6 experts for clarity (ease of understanding). This resulted in 16 items being part of the "PCLD-Complaint-Specific-Assessment (POLCA)", of which 9 items referred to occurrence, and 7 items referring to perceived severity of complaints. Since PCLD is a rare disease, pretesting of the questionnaire in symptomatic PCLD patients was not performed in order not to lose patients for the instrument's validation. The POLCA is available in Supplementary Materials (B) and as an online calculator (http://www.uzleuven.be/en/polca) alongside the LV-index calculator.

Validation group:

The POLCA was administered to only symptomatic PCLD patients (n=61) presenting at 2 different academic centers (University Hospitals KU.Leuven, Leuven and

Université Catholique de Louvain, Brussels) for treatment initiation of which 54 participated in the open-label study to evaluate the safety and efficacy of LAN 90mg, including a dose escalation to LAN 120mg in case of non-responders (clinical trial.gov identifier NCT01315795). A multidisciplinary board consisting of hepatologists, nephrologists, abdominal transplant surgeons, psychologist and social workers discussed each case. Treatment options in this study considered were: *(i)* LAN 90 or 120mg every 4 weeks only; or *(ii)* LAN as a bridge to LTx. The latter group consisted of patients with a high subjective complaint burden due to hepatomegaly and who were considered not to be good candidates for other surgical interventions (e.g. Gigot type III or Mayo Modification D) [29,30]. Patients considered as candidates for combined liver-kidney transplantation (cLTKTx; n=5) were excluded to enhance the objectivity of hepatomegaly related complaints.

The POLCA was administered to all patients prior to the choice of treatment and after 6 months. All data were collected and retrospectively analyzed by a physician who was blinded for the multidisciplinary treatment decision at baseline and the patient's medical characteristics.

Informed consent was obtained from each patient. The use of the POLCA conforms to the ethical guidelines of the 1975 declaration of Helsinki as reflected in the a priori approval by the institution's human research committee.

Reliability and construct validity:

Factor analysis was performed to determine whether the items measure a uni - or multidimensional concept. Next, reliability (internal consistency) of the subscales and total scale was determined by Cronbach's alpha. To test for convergent validity, patients were administered the Short Form 36 Version 2 (SF36V2) at baseline

alongside the POLCA. The SF36V2 is a wildly used, norm-based validated survey that measures health status on 8 health domains (physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, emotional role functioning, social role functioning, mental health). A physical component summary (PCS) and mental component summary (MCS) can be calculated [31,32]. We hypothesized that the POLCA subscales would correlate moderately with the more physically oriented health status domains, with correlation coefficients above 0.3 indicating good convergent validity. In view of known-groups validity, we hypothesized that patients on the waiting list for LTx will have higher POLCA subscale scores than patients not (yet) considered for transplantation.

Criterion validity:

In order to determine the POLCA's concurrent validity, we hypothesized that patients with more complaints also had a larger liver. Therefore, at time of POLCA completion, a CT-scan without contrast enhancement was performed to calculate liver volume and kidney volumes. The CT-scans were performed on different multi-detector CT-scanners: Siemens Somatom Sensation 64 and Siemens Somatom Definition Flash (University Hospitals, KULeuven, Siemens Medical Solutions AG, Erlangen, Germany) and Spiral/Helical CT Brilliance 64 (Philips) (Université Catholique de Louvain, Brussels). Volumes were calculated by using Volume® (Siemens; Erlangen, Germany) by 2 radiologists who were blinded for the questionnaire data and treatment decision [11].

The LV was also 'normalized' to an enlargement index (LV-index) which gives an idea how many times the liver is enlarged for the individual patient (LV-index=liver

volume (mL) (CT-scan)/((706.2*body surface area)+2.4)) [33]. We anticipated a moderate to strong correlation (r>0.50) as proof of concurrent validity.

Responsiveness:

We hypothesized that changes in subscales of the questionnaire between baseline and month 6 were detectable and significant as a result of the pharmacological treatment. In addition, based on our previous observations, we also hypothesized that a reduction of ≥120mL in LV after 6 months of SA-treatment results in a more pronounced effect on the perceived complaints [12].

Statistical analysis

Analysis of internal consistency was evaluated with Cronbach' alpha, with value >0.7 and <0.9 indicating excellent reliability. To analyze whether they were at least some correlations amongst the 16 POLCA items so that coherent factors are allowed to be identified, factorability was assessed by measures of sampling adequacy (Kayser-Mayer-Olkin>0.5). Factor analysis on Eigenvalues was performed to identify subscales and remove suboptimal items, in which an Eigenvalue < 1 does not have enough total variance explained to represent an unique factor. To facilitate the interpretation of extracted correlated factors, Promax rotation was used. Differences in characteristics between groups were analyzed by an independent t-test (two tailed) or Mann-Whitney U Test, where appropriate. In order to evaluate responsiveness of the POLCA over time, a paired sample t-test was used. To describe correlations, non-parametric testing by Spearman was performed. To compare percentages of observations between groups, Chi-square testing was used. Data are presented as mean with standard deviation (SD) or standard error (SE), unless otherwise

specified. All statistics were performed in SPSS version 19 (SPSS Inc, Chicago, IL, USA). A p-value< 0.05 was considered as statistically significant.

Results

Study population

The characteristics of the creation and validation group are presented in Table 1.

Creation group: Data from 68 patients who were treated because of symptomatic PCLD between 1997 and 2010 were extracted. There were 60 women (88%). 60 patients were diagnosed with ADPKD. 49 women and 11 men were diagnosed with ADPKD.

Validation group: Between January 2011 and August 2013, 61 symptomatic PCLD patients completed the POLCA at baseline. All patients were started on SA of which 14 were multidisciplinary evaluated as LTx candidates. Patients were given LAN 90mg or 120 mg/4 weeks during at least 6 months. Patients considered as LTx candidates were significant younger than patients in the other group, in which ages were respectively 47y (SD:8.1) and 52y (SD:8) (Independent t-test *p*=.04). Mid-upper arm circumference (cm) for both groups were respectively: 24.8 (SD: 2.8) and 25.8 (SD: 2.8) (p=0.3).

Validity

Factor analysis and reliability:

Kayser-Meyer-Olkin measure of Sampling adequacy was 0.73. Factor analysis yielded 3 subscales related to complaint experience explaining 55% of the total variance, i.e. *(i)* gastro-oesophagal reflux disease (GERD) related complaints (4 items), *(ii)* impact on food intake (2 items); and *(iii)* perception of enlarged liver

volume (3 items). Cronbach's alpha for the 9 items measuring symptom experience was 0.81, with alpha's for the 3 subscales being 0.81, 0.74 and 0.64 respectively, and 0.86 for the total scale, indicating satisfactory reliability. Pattern matrix clustered all items that highly loaded on each factor. Factor loading, expressing the correlation of the item with the factor, was at least 0.39. Figure 1 represents the items referring to the different subscales. Sum scores for the 3 factors and for the 7 items referring to 'severity of perceived illness' were calculated and used for further statistical analysis. Minimum-maximum scores for each subscale were: *(i)* severity of perceived illness: 0-35; *(ii)* GERD related complaints: 0-20; *(iii)* impact on food intake: 0-10; *(iv)* perception of enlarged liver volume: 0-15. Spearman correlation coefficients between all 4 item groups ranged from 0.24 to 0.45. The higher the score, the higher the complaint experience or severity.

Convergent validity:

All subscales showed moderate to good correlations with some SF36V2 subscales, as well as with the Physical Component Summary (Table 2). Spearman correlations ranged from -0.3 to -0.7, providing evidence for convergent validity of the POLCA. Correlations with the other subscales, i.e. emotional role, mental health as well as with the Mental Component Summary, were weak and not significant.

Known-groups validity:

With the exception of impact on food intake, all subscale sum scores were significantly lower in symptomatic patients treated with SA only (n=47) compared to patients listed for LTx (n=14), indicating known-groups validity. The LV-index in both groups was respectively 4 (SD:1.5) and 5 (SD:1.7) (Independent t-test; p=.04),

reflecting that a more enlarged liver induces more complaints. The results of the POLCA subscales and SF36V2 of both groups are given in Table 3.

Concurrent validity:

We could not observe significant linear correlations between total scores of POLCA subscales and LV-index or liver volume at baseline, indicating a lack of concurrent validity. Health domains and summary scores of the SF36V2 did not correlate with liver volumes either.

Responsiveness:

For 47/61 patients (77%) (LTx group: n=7; no-LTx group n=40), paired observations (i.e. baseline and month 6) regarding LV, SF36V2 and POLCA were available.

The baseline characteristics of these patients were: *(i)* women (n=43); *(ii)* ADPKD (n=40); *(iii)* age 51y (SD:1.2); *(iv)* LV-index: 4.1 (SE:0.2). Dropout reasons (n=14) were: underwent LTx (n=5); SA related side effects (n=2); missing item data (n=7).

Overall absolute LV reduction was -116mL (SD:411). Despite a borderline significant increase in general health (p=0.06) and physical component summary (p=0.07), none of the SF36V2 health domains significantly changed after 6 months. In contrast, two of the 4 POLCA subscales significantly decreased over time, indicating responsiveness to treatment, with scores on the 3th and 4th subscale being borderline significant (Figure 2).

LTx patients versus no-LTx patients:

The POLCA changes in time in the no-LTx group (n=40) and the LTx -group (n=7) were different and are given in figure 3. In the LTx group, LV increased with 90mL (SE:246) whereas in the no LTx group LV decreased with 246mL (SE: 52) (p=0.1).

Patients with changes in LV ≥120mL versus <120mL:

In 20/47 (43%) a reduction of at least 120mL in LV was observed, which was in accordance with a significant reduction in total scores of 2 POLCA subscales e.g. *(i)* severity of perceived illness and *(ii)* GERD related complaints (paired t-test; respectively: p=0.04 and 0.001). The relative reductions in means of total scores were numerical more pronounced compared with the patient group not meeting this volume reduction (Table 4).

Discussion

In the present study we developed and psychometrically validated the POLCA questionnaire, specifically designed to capture the presence and the severity of hepatomegaly-related complaints from the perspective of patients with symptomatic polycystic liver disease. Complaints expressed by PCLD patients and their interpretation by clinicians in terms of severity and impact on the health related quality of life (HRQL) is subjective, yet, highly relevant as decisions on medical treatment and even indication for LTx in PCLD, are partially based on the severity of complaints.

Because of their subjective nature, it is crucial that complaints related to hepatomegaly can be assessed in a standardized, validated way. The POLCA is an easy to use, disease-specific complaint instrument that might assist in determining the best care for symptomatic patients as it is reliable, valid and sensitive, as shown by the present study.

Available treatment options aim to reduce LV, either by the administration of SA or (non)-Tx surgery, and alleviate its associated complaints. Studies thus far only evaluated HRQL in relation to cyst fenestration and LTx as an outcome in PCLD

patients [23,24,34]. Although improvement was seen in some HRQL domains using the SF36 version1 in the two randomized placebo controlled trials, the extent to which SA ease complaints using non-disease specific questionnaires remained unclear [7,8]. In another study, patients were asked whether their complaints changed after 6 months of SA treatment, but no validated questionnaire documenting changes in specific complaints was used [11]. By using chart review, literature review and expert input, we ensured that the POLCA evaluates all complaints that patients with PCLD can experience as a result of hepatomegaly as proof of content validity. Construct validity was demonstrated by the moderate to high correlations with the Physical Composite score of the SF36 V2, reflecting the disability caused by complaints on patients physical functioning. No significant correlation with the Mental Composite Score was observed, suggesting that the higher symptom burden was not the result of mental problems such as e.g. depression. Furthermore, the Physical composite score was significantly lower in LTx-group compared to no-LTx patients. There was in this subgroup also no difference in Mental Composite scores. These results are important as one wants to be sure that complaints experienced are the result of a medical condition such as hepatomegaly, and not by underlying mental problems.

We could not observe a linear correlation between POLCA scores and LV, which is from a clinical point of view not unexpected. We demonstrated that especially young women with higher LV-indices displayed more complaints. In this regard, we postulate that changes in LV per time unit rather than a given LV account for complaint experience and severity.

As proof of known-groups validity, we further demonstrated *(i)* that patients listed for LTx had significantly higher scores on all POLCA subscales, which was in

accordance to a significant more pronounced enlargement of the liver. In addition, we founded that the POLCA changes in time under SA treatment were different for LTx candidates *versus* those who were not. In this regard, the POLCA scores and the changes in time could play a role in the multidisciplinary approach for treatment decision of symptomatic PCLD patients, as the impact of their hepatomegaly on their symptom experience and impact on daily functioning might help to better determine the timing of starting medical therapy and assess its efficacy and effectiveness, or considering (non)-Tx surgery.

This study demonstrates that the POLCA is able to standardize complaints in PCLD patients, on the other hand we are convinced that also other factors play their role in the orchestration of the therapeutic approach and that the management of PCLD requires a multidisciplinary approach. A schematic overview of an objective assessment of symptomatic PCLD patients is presented in Figure 4.

In this stadium of validation of this self report instrument, we excluded the data of 5 patients considered as cLTKTx candidates to construct the POLCA. Since the decision for single KTx *versus* cLTKTx in ADPKD with end stage renal disease is an important issue, we also analyzed the data of these 5 patients separately in view of our findings (for details; see Supplementary Materials C). Their results suggest that the POLCA might also be of value in this subpopulation. However, the group was too small to draw firm conclusions.

The following study limitations should be acknowledged. First, this was not a placebo controlled trial and patients in the validations group were aware of the potential effect of SA treatment at study enrollment. Second, the sample size used to validate the POLCA is relatively small. PCLD, however, is a rare disorder, limiting the possibility of large samples. Third, no a-symptomatic patients were available, as the study was

conducted at tertiary referral centers. No registry of patients exists today, limiting our options to reach out to other (a)symptomatic patients. Fourth, there has been some debate as whether or not to include dyspnea as a hepatomegaly-related complaint. Given that there is no correlation with objective lung function testing and that dyspnea can be related to other extra-hepatic causes, it was decided not to include this complaint. Fifth, although 3 questions of the POLCA refer to nutrition (i.e. appetite, early satiety, and impression on body weight evolution), objective assessment of the nutritional status in PCLD is warranted. The mid-upper arm circumference is currently used as a gold standard to assess malnutrition as it reflects lean body mass. However, other more objective techniques should be evaluated in the future such as the calculation of total muscle mass at lumbar 3 level to assess the prevalence of sarcopenia and identify PCLD specific risk factors for poor nutrition complementary to the POLCA [35,36]. Finally, although validity was tested in a comprehensive way, other hypotheses could have been considered.

The validation of self-report instruments is however a complex, continuous process; and there is obviously a need for further studies. Multicenter studies need to be assessed in order to confirm our findings with the inclusion of other treatment options considered in symptomatic PCLD such as patients who are candidates for combined liver and kidney transplantation and in the selection and follow-up of patients who are candidates for non-LTx surgery.

In conclusion, the POLCA is an easy, reliable, valid and sensitive self-report questionnaire to evaluate the presence and severity of hepatomegaly-related complaints of patients with PCLD. This questionnaire can be embedded both in research and clinical care, as it *(i)* allows tracking the natural evolution of

hepatomegaly-related complaints over time; *(ii)* can guide treatment decisions; and *(iii)* facilitates the evaluation of treatment effects over time.

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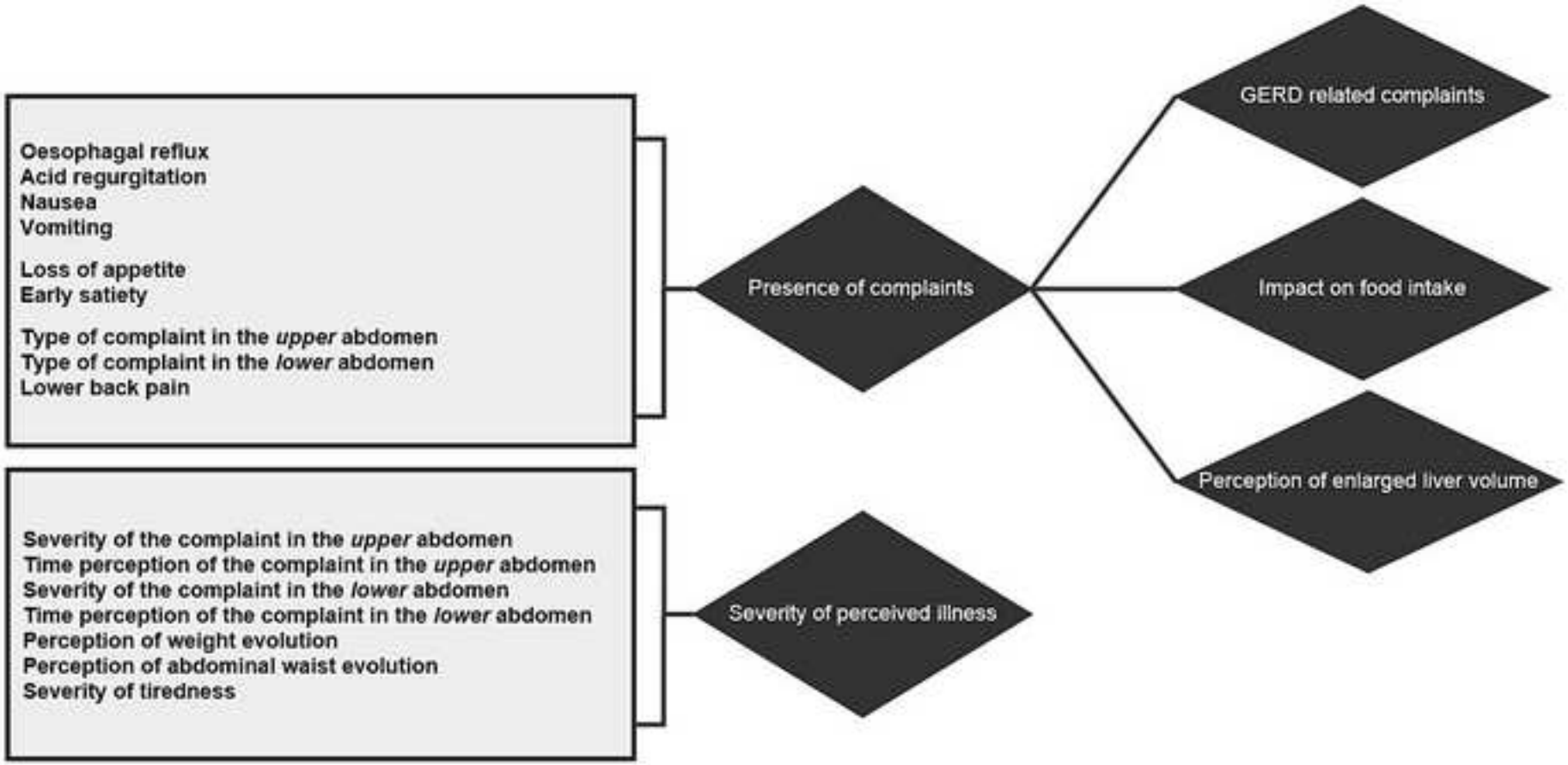
Figure legends

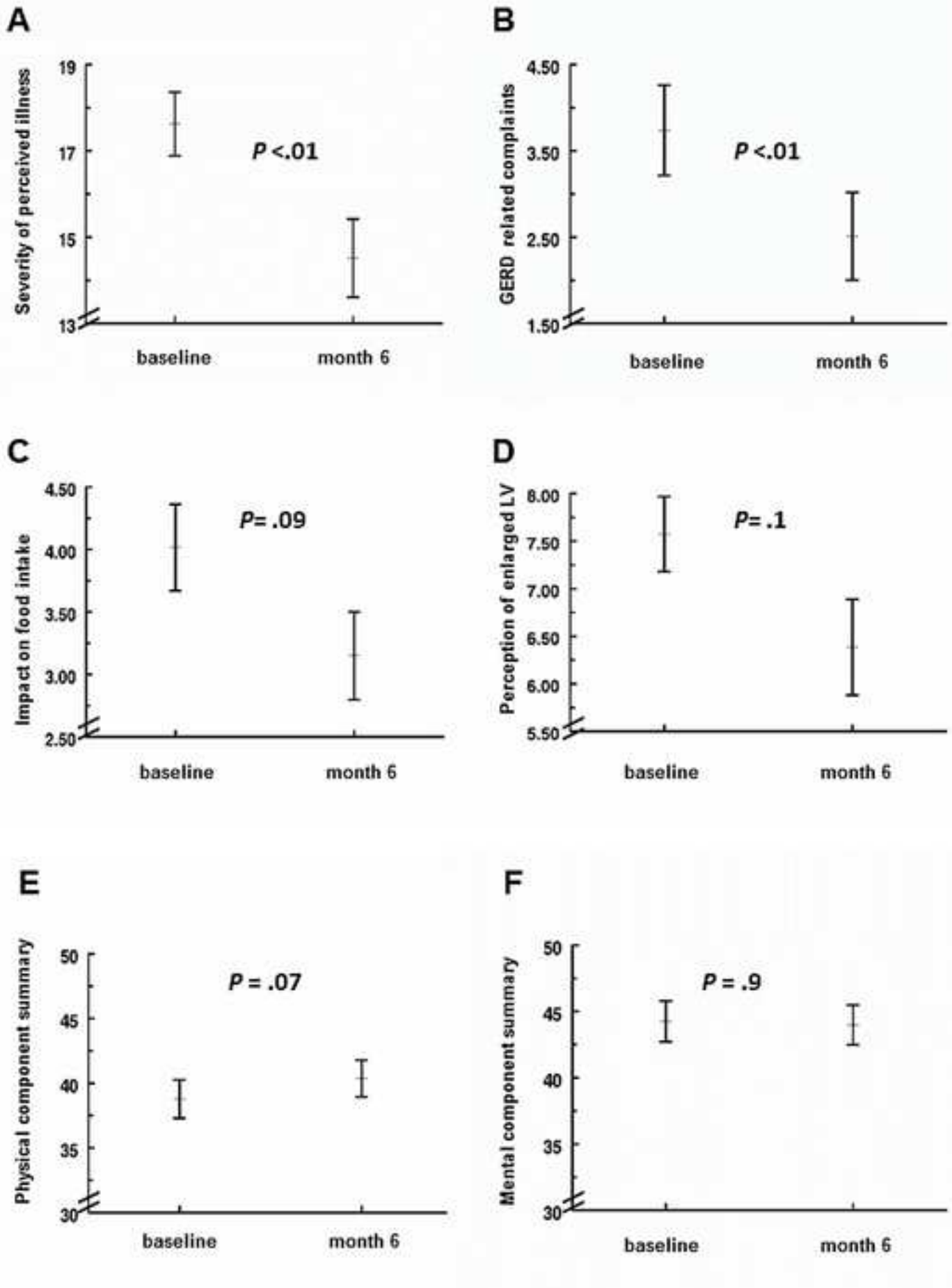
Fig. 1. Overview of the POLCA with the 16 items. According to the conceptual framework 9 items reflect presence (item scoring: 0= symptom not occurring; 5= symptom present all the time) and 7 items represent severity of perceived illness (item scoring: 0= not; 5= extreme severe). Factor analysis on complaint experience recognized 3 subscales. The minimum and maximum scores for each subscale presented are: *(i)* severity of perceived illness: 0-35 (7 items) *(ii)* Gastro-oesophagal reflux disease related complaints: 0-20 (4 items), *(iii)* Impact on food intake: 0-10 (2 items); *(iv)* Perception of enlarged liver volume: 0-15 (3 items).

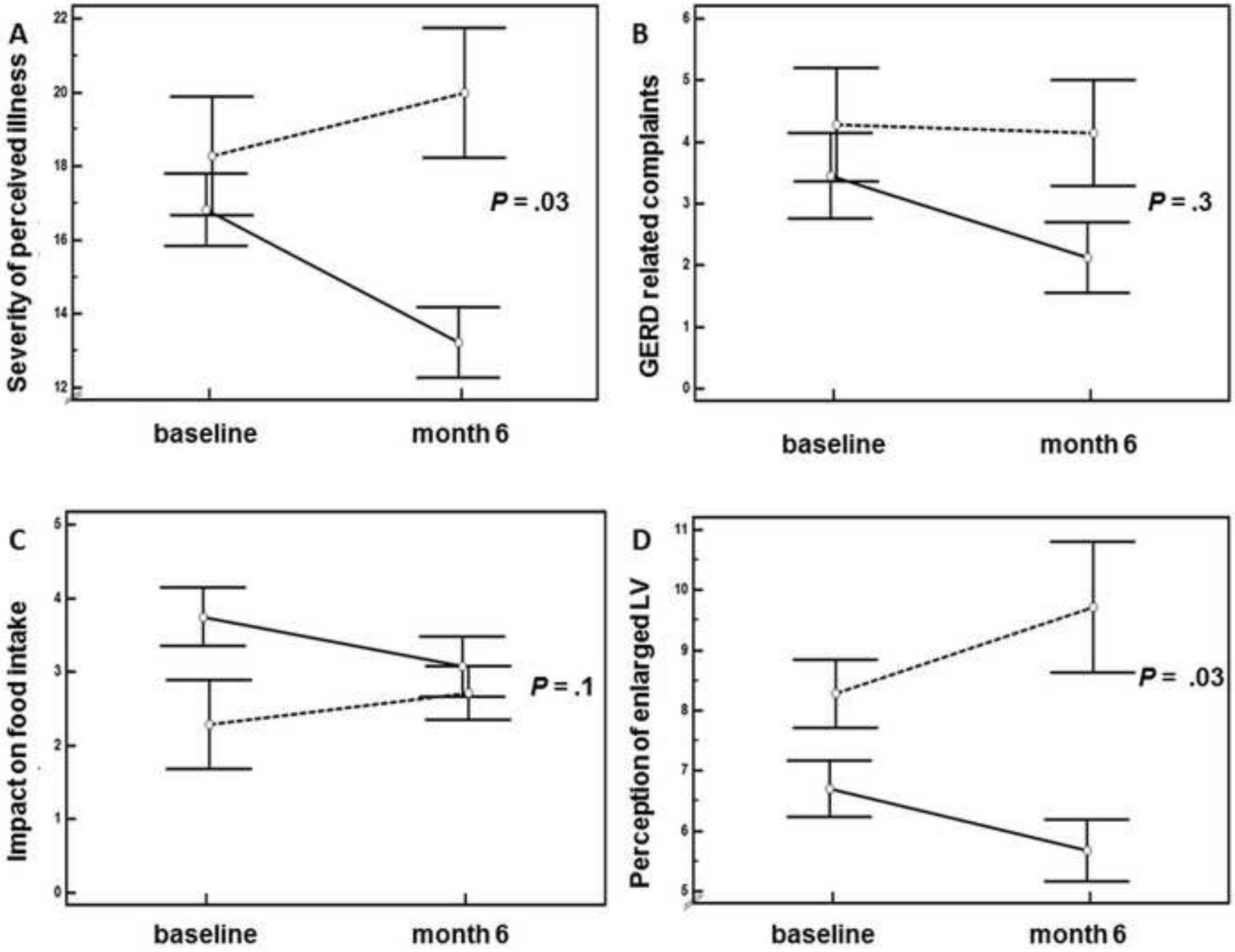
Fig. 2. Overall responsiveness analysis of the 4 POLCA subscales and the 2 summary components (SF36V2) (n=47). (A) Severity of complaints (range: 0-35); (B) Gastro-oesophagal reflux disease (GERD) related complaints (range: 0-20); (C) Impact on food intake (range: 0-10); (D) Perception of enlarged liver volume (range: 0-15); (E) Physical component summary (range: 0-100) (F) Mental component summary (range: 0-100). Data presented as mean (± standard error of mean).

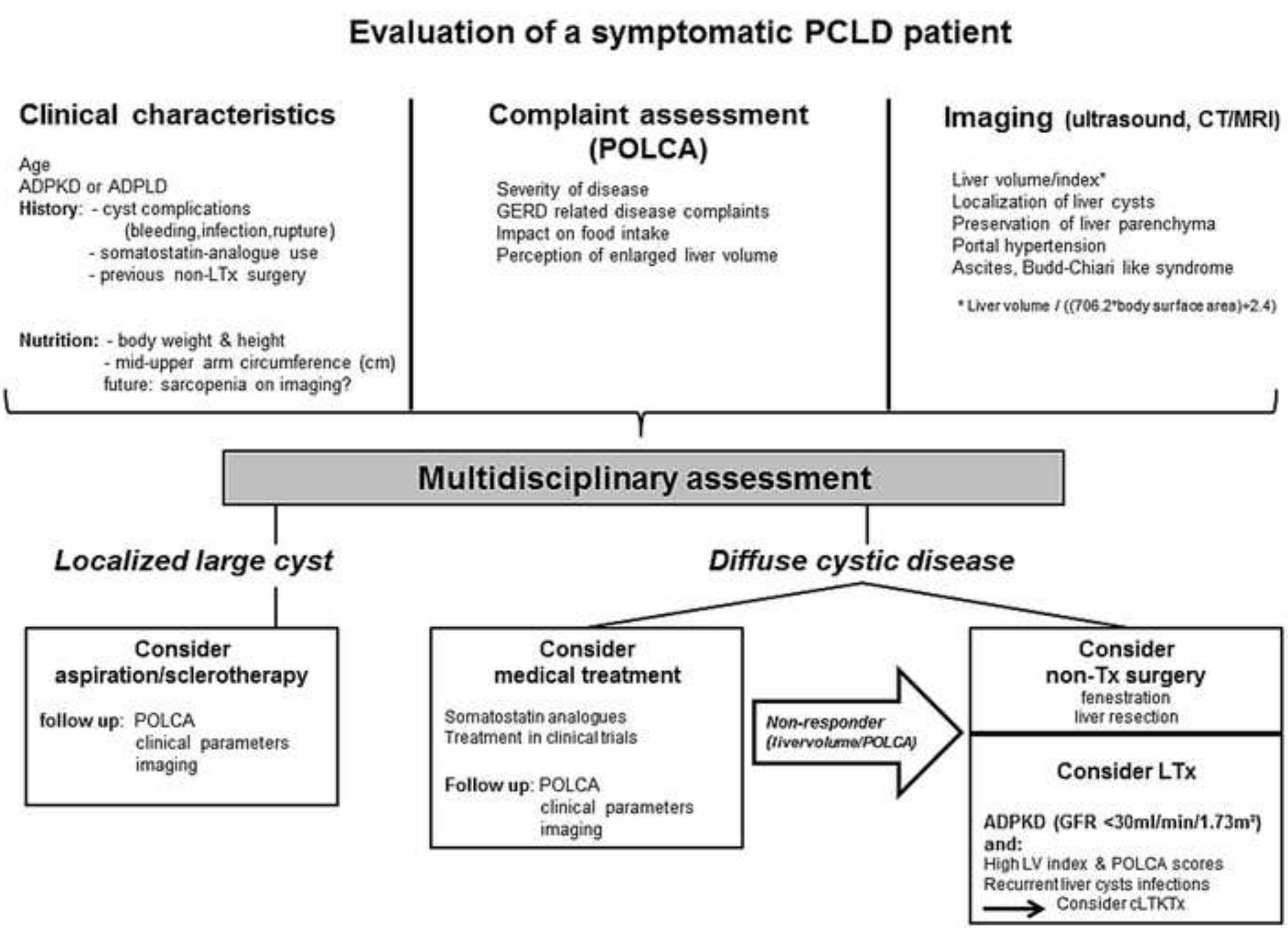
Fig. 3. Paired observations of the 4 POLCA subscales in patients listed for LTx (dashed line: n=7) and patients receiving somatostatin analogues only (full line; n=40). (A) Severity of complaints (range: 0-35); (B) Gastro-oesophagal reflux disease (GERD) related complaints (range: 0-20); (C) Impact on food intake (range: 0-10); (D) Perception of enlarged liver volume (range: 0-15). Data presented as mean (± standard error of mean). P value represents the group*factor interaction.

Fig. 4. Flow chart for an objective assessment of patients with symptomatic PCLD and therapeutic possibilities.









Tables

Table 1 Baseline demographic and clinical characteristics of the study population.

Characteristics	Creation group (n=68)	Validation group (n=61)
ADPKD/ ADPLD	60/8	50/11
Age (Y) (SD) **female (Y) (SD)** **male (Y) (SD)**	52 (±7.7) 51.5 (±7.9) (n=60) 56 (±6) (n=8)	51 (±8.5) 50 (±8) (n=55) 57.5 (±9.5) (n=6)
Age diagnosis (Y) (SD)	NA	36 (±10.5)
Age onset complaints (Y) (SD)	NA	47 (±11)
Liver volume (mL) (IQR)	4355 (2906;6200)	4945 (3814;7300)
Liver volume-index (SD)	3.8 (±1.7)	4.2 (±1.6)
Kidney volume mL (IQR) (ADPKD)	887 (417;1792) (n=60)	1126 (586;1806) (n=55)
Glomerular filtration rate (MDRD) **ADPKD ml/min/1.73m² (IQR)** **ADPLD ml/min/1.73m² (IQR)**	 48 (17;71) 82 (73;96)	 58 (43;75) 85 (71;91)
MUAC (cm) (SD)	NA	25.5 (2.8)

Legend: ADPKD: Autosomal Dominant Polycystic Kidney disease; **ADPLD**: Autosomal Dominant Polycystic Liver Disease; **NA:** not assessed; **GFR**: glomerular filtration rate; **MDRD**: Modification of Diet in Renal Disease
Liver volume index = LV (imaging)/((706.2 x body surface area)+2.4); **MUAC:** mid-upper arm circumference

Table 2 Spearman correlations between POLCA and SF36V2 health domains.

POLCA / SF36V2	Severity of perceived illness	GERD related complaints	Impact on food intake	Perception of enlarged LV
Physical functioning	-0.3**	NS	-0.27*	-0.3**
Physical role functioning	-0.4***	-0.5***	-0.26*	-0.56***
Bodily pain	-0.4***	-0.47***	NS	-0.6***
General health	-0.33**	-0.48***	NS	-0.473***
Vitality	-0.32**	NS	NS	-0.35**
Social functioning	-0.49***	NS	-0.4***	-0.281*
Emotional role functioning	NS	NS	NS	NS
Mental health	NS	NS	NS	NS
Physical component summary	-0.45***	-0.55***	-0.34**	-0.53***
Mental component summary	NS	NS	NS	NS

Legend: GERD: gastro-oesophagal reflux disease; **LV**: liver volume; **NS**: not significant.
*p<.1; **p<.05; ***p<.01.

Table 3 Comparison of POLCA subscales and SF36V2 health domains between patients not (yet) considered as LTx candidates (no-LTx group) *versus* patients considered as LTx candidates (LTx group).

	No-LTx group (n=47)	**LTx group (n=14)**	***P***
POLCA			
Severity of perceived illness	16.8 (±6)	20.3 (±4.3)	0.049*
GERD related complaints	2 (0.25;4)	5 (2;7)	0.03**
Impact on food intake	3.7 (±2.5)	4.9 (±3.2)	0.15*
Perception of enlarged LV	7(5-9)	8 (8-11)	0.006**
SF36V2			
Physical component summary	42 (±9.7)	33 (±8.3)	0.007*
Mental component summary	45.5 (41;53)	41 (28;52.5)	0.2

Legend: **LTx**: liver transplantation; **GERD**: gastro-oesophagal reflux disease; **LV**: liver volume
Data presented as mean (SD) and median (IQR) where appropriate.
*Independent t-test; ** Mann-Whitney U statistic.

Table 4 Mean scores (±SD) of the POLCA subscales at baseline and after 6 months of treatment with lanreotide. A more pronounced relative reduction in differences of mean in all subscales can be observed in patients with a reduction ≥120mL after 6 months.

POLCA	Change liver volume ≥120mL n=20			Change liver volume <120mL n=27			
	Baseline	**Month 6**	**Change**	**Baseline**	**Month 6**	**Change**	**P***
Severity of perceived illness	15.2 (±5.4)	12.4 (±6)	**-19%**	18.5 (±6.0)	16 (±6.0)	**-13%**	NS
GERD related complaints	2.2 (±2.2)	0.9 (±1.1)	**-59%**	4.8 (±4.9)	3.7 (±4.1)	**-23%**	.03
Impact on food intake	3.3 (±2.1)	2.7 (±2.1)	**-18.2%**	3.9 (±2.6)	3.5 (±2.6)	**-10.3%**	NS
Perception of enlarged LV	6.4 (±2.8)	5.5 (±3.3)	**-14%**	7.5 (±3)	7 (±3.5)	**-6%**	NS

Legend: GERD: gastro-oesophagal reflux disease; **LV**: liver volume; **NS**: not significant.
* Chi-square.